Abstract of the Disclosure

In proteomic research, it is often necessary to screen a large number of polypeptides for the presence of stable structure. Described herein are methods (referred to as MALDI MS-HX and SUPREX) for measuring the stability of proteins in a rapid, high-throughput fashion. The method employs hydrogen exchange to estimate the stability of quantities of unpurified protein extracts, using matrix-assisted laser desorption/ionization (MALDI) mass spectrometry. A method of quantitatively determining the stability of a test protein under native conditions is disclosed. The method includes the steps (a) providing a test protein; (b) contacting the protein with an exchange buffer comprising a denaturant and deuterium, the exchange buffer having a denaturant concentration; (c) contacting the test protein with a mass spectrometry matrix medium; (d) determining a change in mass of the test protein by mass spectrometry; (e) varying the denaturant concentration of the exchange buffer; (f) repeating steps (a)-(e) a desired number of times; and (g) quantitatively determining protein stability based on the change in mass of the test protein as a function of denaturant concentration, whereby the stability of a test protein under native conditions is quantitatively determined.